UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/633,407	08/01/2003	Douglas W. Losordo	58098 (71417)	6007

21874 7590 01/23/2008
EDWARDS ANGELL PALMER & DODGE LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
O'HARA, EILEEN B	

ART UNIT	PAPER NUMBER
1646	

MAIL DATE	DELIVERY MODE
01/23/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/633,407	LOSORDO ET AL.	
	Examiner	Art Unit	
	Eileen B. O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-76* is/are pending in the application.

4a) Of the above claim(s) *4-7,10,14-16,20,22,23,28,29,35,43-65 and 69-74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,8,9,11-13,17-19,21,24-27,30-34,36-42,66-68,75 and 76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/ are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-76 are pending in the instant application. Claims 75 and 76 have been added as requested by Applicant in the Paper filed November 1, 2007.

Claims 4-7, 10, 14-16, 20, 22, 23, 28, 29, 35, 43-65 and 69-74 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-3, 8, 9, 11-13, 17-19, 21, 24-27, 30-34, 36-42, 66-68, 75 and 76 are currently under examination.

Maintained Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2.1 Claims 1-3, 8, 11-13, 17-19, 21, 24-27, 30-33, 36-42 and 66-68 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants on pages 13-15 of the response traverse the rejection, and cite in re Wertheim and a section from M.P.E.P. 2163. However, the quote Applicants cite from M.P.E.P. 2163 is isolated and out of context, and does not adequately address the requirements of written

description. Possession of some form of physical compound is required . The full paragraph states:

> "An applicant ma y also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. Enzo Biochem, 323 F.3d at 964, 63 USPQ2d at 1613. For example, the presence of a restriction enzyme map of a gene may be relevant to a statement that the gene has been isolated. One skilled in the art may be able to determine whether the gene disclosed is the same as or different from a gene isolated by another by comparing the restriction enzyme maps. In contrast, evidence that the gene could be digested with a nuclease would not normally represent a relevant characteristic since any gene would be digested with a nuclease. Similarly, isolation of an mRNA and its expression to produce the protein of interest is strong evidence of possession of an mRNA for the protein. For some biomolecules, examples of identifying characteristics include a sequence, structure, binding affinity, binding specificity, molecular weight, and length. Although structural formulas provide a convenient method of demonstrating possession of specific molecules, other identifying characteristics or combinations of characteristics may demonstrate the requisite possession. >As explained by the Federal Circuit, "(1) examples are not necessary to support the adequacy of a written description; (2) the written description standard may be met ... even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." Falkner v. Inglis, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006). See also Capon v. Eshhar, 418 F.3d at 1358, 76 USPQ2d at 1084 ("The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes" where the genes were novel combinations of known DNA segments.).< For example, disclosure of an antigen fully characterized by its structure, formula, chemical name, physical properties, or deposit in a public depository provides an adequate written description of an antibody claimed by its binding affinity to that antigen. Noelle v. Lederman, 355 F.3d 1343, 1349, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (holding there is a lack of written descriptive support for an antibody defined by its binding affinity to an antigen that itself was not adequately described). Additionally, unique cleavage by particular enzymes, isoelectric points of fragments, detailed restriction enzyme maps, a comparison of enzymatic activities, or antibody cross-reactivity may be sufficient to show possession of the claimed invention to one of skill in the art. See Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966 ("written description" requirement may be satisfied by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set

forth the claimed invention"). A definition by function alone "does not suffice" to sufficiently describe a coding sequence "because it is only an indication of what the gene does, rather than what it is." Eli Lilly, 119 F.3 at 1568, 43 USPQ2d at 1406. See also Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991)). **An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.")."**

This last situation, that of claims to inhibiting an activity by administering non-steroidal compounds, is analogous to the instant claims, since the instant claims are drawn to methods of treatment with compounds with no disclosed structure whatsoever. Therefore, only Y27632, but not the full breadth of the claims, meet the written description provision of 35 U.S.C. §112, first paragraph.

2.2 Claims 1-3, 8, 9, 11-13, 17-19, 21, 24-27, 30-34, 36-42 and 66-68 remain rejected, and new claims 75 and 76 are rejected, under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record in the previous office action, and below.

Applicants traverse the rejection on pages 15-19 of the response, and submit that the examples provided in the specification clearly teach the methods of the claims. Applicants assert that example 14 shows that *in vivo* increase in endothelial cell proliferation and increase in blood vessel formation results from reducing ezrin activity, and example 16 shows that blocking RhoA kinase activity relieves ezrin/TNF mediated inhibition of endothelial cell proliferation, and that the claims are enabled from the examples in the specification correlating *in vitro* and *in vivo* experiments. Applicants cite *Cross v. Iizuka*:

> [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence.

Applicants' arguments have been fully considered but are not deemed persuasive. First, example 14 is not an experiment in which ezrin activity is reduced by treatment of any compound; the experiment was transplantation of endothelial cells that had no ezrin activity at all, which is a different biological situation. *Cross v. Iizuka* is not applicable to the instant claims, since that case dealt with utility of claims directed to imidazole derivative compounds which inhibit the synthesis of thromboxane synthetase, and not to methods of treatment with any compounds, and the U.S. Court of Appeals agreed with the Board that:

> "tests evidencing pharmacological activity may manifest a practical utility even though they may not establish a specific therapeutic use."

In that case the claims were directed to pharmaceutical compounds, while in the instant case they are directed towards methods of modulating endothelial cell proliferation by decreasing ezrin activity or by enhancing endothelial cell proliferation or inducing formation of new blood

vessels in a mammal, by decreasing ezrin activity *in vivo* by administering an azrin modulating agent, which may be an inhibitor of Rho kinase. While the *in vitro* and *in vivo* data in the specification indicates that reducing ezrin activity could be beneficial in inducing endothelial cell proliferation, the art shows that methods of treatment of animals are very complex and are not predictable.

Applicants on pages 17-18 assert that claimed method is irrelevant to the question of enablement, and argue that the Shibata reference is inconclusive as to whether ezrin activity is affected, since Shibata et al. state that there is no direct method available to assay Rho-kinase activity in vascular samples, and it is possible that inhibition of other serine-threonine protein kinases in addition to Rho-kinase may have contributed to the effects of Y27632 observed in the study, and because Rho is not the only possible activator of Rho-kinase, it is possible that upstream pathways other than Rho would activate Rho-kinase in injured artery, and because Y27632 was systemically administered for a long time in the present study, the possibility of the involvement of indirect systemic effects, such as neurohumoral effects, cannot be excluded.

From this Applicants assert that it is unclear from Shibata whether the administration of Y27632 decreased Rho-kinase activity and, consequently, ezrin activity, nor does their experiment rule out the possibility that other effects may mask the effect of decreasing ezrin activity *in vivo,* and in particular, Shibata discuss the possibility of other systemic effects due to their experimental design.

Applicants' arguments have been fully considered but are not deemed persuasive. Applicants have claims directed to administration of Y27632 to enhance EC proliferation and reduce blood vessel damage in a mammal, yet Shibata et al. demonstrated that Y27632 had the

opposite effect, that of inhibiting early neointimal lesion formation. In the final paragraph on page 289, Shibata et al. state:

> "In conclusion, a Rho-kinase inhibitor, Y27632, inhibited early neointimal lesion formation, probably by suppressing early SMC migration into the intima and prevented neointima formation in the later phase by enhancing neointimal SMC apoptosis. Thus, a role of Rho-kinase in neointima formation is suggested by regulation of SMC migration and apoptosis. Finally, the present study may provide insight into the possible treatment strategy to prevent progression of atherosclerosis by inducing apoptosis in neointimal SMCs during the remodeling process after vascular injury."

Additionally, even if ezrin activity were reduced in Shibata et al., other compensatory mechanisms may occur, which could negate the effects of inhibition of Rho kinase, as discussed by Shibata et al.

Van Nieuw Amerongen et al., *Arteriosclerosis, Thrombosis, and Vascular Biology.* 2003;23:211, explored the involvement of RhoA/Rho kinase signaling in VEGF-induced cell migration and angiogenesis in vitro. On page 211 of Van Nieuw Amerongen et al. it is stated:

"Methods and Results— VEGF induced the activation of RhoA and recruited RhoA to the cell membrane of human ECs. This increase in RhoA activity is necessary for the VEGF-induced reorganization of the F-actin cytoskeleton, as demonstrated by adenoviral transfection of dominant-negative RhoA. Rho kinase mediated this effect of RhoA, as was demonstrated by the use of Y-27632, a specific inhibitor of Rho kinase. Inhibition of Rho kinase prevented the VEGF-enhanced EC migration in response to mechanical wounding but had no effect on basal EC migration. Furthermore, in an in vitro model for angiogenesis, inhibition of either RhoA or Rho kinase attenuated the VEGF-mediated ingrowth of ECs in a 3-dimensional fibrin matrix.

Conclusions— VEGF-induced cytoskeletal changes in ECs require RhoA and Rho kinase, and activation of RhoA/Rho kinase signaling is involved in the VEGF-induced in vitro EC migration and angiogenesis."

Therefore Van Nieuw Amerongen et al. demonstrates that in some situations such as wounding, inhibition of Rho kinase prevents EC migration and angiogenesis.

From the results in the instant disclosure, one skilled in the art would expect that decreasing ezrin activity should reduce the severity of blood vessel damage when a mammal is exposed to conditions conducive to damaging the blood vessels. However, the art teaches that complex biological systems are unpredictable, especially when there are many different pathways involved in processes such as modulation of endothelial cell proliferation in formation of new blood vessels or reducing severity of blood vessel damage in mammals.

In the instant case, the disclosure and art are not predictive of treating a mammal with a compound that decreases ezrin activity, for the reasons discussed in the previous Office Action, and above. For these reasons, the rejection is maintained.

It is believed that all pertinent arguments have been answered.

Conclusion

3. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nichol can be reached at (571) 272-0835.

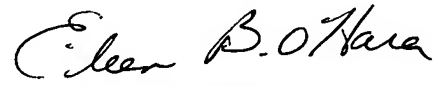
The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara, Ph.D.

Patent Examiner



EILEEN B. O'HARA
PRIMARY EXAMINER